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TREATMENT OF SYPHILIS

COMPARISON OF THE NUMBER OF DAYS' HOSPITAL TREATMENT REQUIRED FOR PATIENTS SUFFERING WITH SYPHILIS, WITH AND WITHOUT THE USE OF SALVARSAN OR NEOSALVARSAN

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By W. G. STIMPSON, Assistant Surgeon General, United States Public Health Service.

Between July 1, 1913, and January 1, 1914, 226 syphilitic patients were treated with salvarsan or neosalvarsan in the 21 hospitals and other stations of the service. To this number have been added 204 cases treated before this period, making a total of 430. These patients were in hospital 5,727 days, or an average of 13.31 days for each patient. The records of the stations show that before the use of these remedies an average of 29.14 hospital days' treatment was required for each patient, so that their use has diminished the average number of days' treatment by 15.73 days.

These facts are shown very clearly by the following table:

Table showing the average number of days' hospital treatment required for patients suffering with syphilis with and without the use of salvarsan or neosalvarsan.

Name of station.	Cases treated without salvarsan or neosalvarsan.			Cases treated with salvarsan or neosalvarsan.		
	Cases treated.	Days relief.	Average duration of treatment.	Cases treated.	Days relief.	Average duration of treatment.
Baltimore	27	1,221	45.22	20	482	24.10
Boston	59	1,812	30.70	36	943	26.20
Buffalo	2	26	13.00	14	108	7.70
Cairo	36	677	18.80	1	24	24.00
Cleveland	31	908	29.29	2	3	1.50
Detroit	13	134	10.30	11	55	5.00
Honolulu	12	732	61.00	4	214	53.50
Key West	5	173	34.60	2	100	50.00
Louisville	90	2,166	24.00	1	2	2.00
Mobile	5	298	59.60	20	384	19.20
New Orleans	103	2,978	28.91	84	1,366	16.26
Norfolk	126	1,953	15.50	35	333	9.50
Philadelphia	.....	.....	.....	29	395	13.40
Providence	.....	.....	.....	9	67	7.40
Port Townsend	34	1,451	42.67	4	50	12.50
St. Louis	13	360	27.69	5	71	14.20
San Francisco	65	2,496	38.40	39	298	7.60
Seattle	15	225	17.00	94	236	2.50
Savannah	15	698	46.50	14	437	31.30
Vineyard Haven	20	810	40.50	2	79	39.50
Wilmington	28	1,184	42.30	4	80	20.00
Total	699	20,302	29.04	430	5,727	13.31

The following notes on the treatment of syphilis and reports of cases have been received from officers in charge of stations:

Boston, Mass.—In the case of every patient manifesting any symptoms of specific infection a specimen of blood is taken and

tested to ascertain if the Wassermann reaction is present. For the most part this is done by sending the specimens to the Hygienic Laboratory in Washington. If such report is returned negative, and the case remains suspicious, or if the specimen is rendered valueless by transportation through the mail, either because the tube becomes broken or the blood becomes laked from the shaking it receives in transit, the blood is tested in Boston at the Harvard Medical School.

A large majority of patients treated with neosalvarsan are those in whom the blood has given a positive Wassermann reaction. In some of the cases where no doubt as to the diagnosis of luetic infection exists, neosalvarsan is administered after a specimen of blood is taken to be tested but before the report on it is received.

Salvarsan itself is not used. The greater amount to be given, the severe reaction to it by some patients (headache, vomiting, diarrhea, etc.), the longer time consumed in preparing it—that is, in dissolving it and in alkalinizing the solution—and its supposedly deleterious effect on the interior of the blood vessels, due to its not being thoroughly dissolved, all of these disadvantages militate against the use of salvarsan. On the other hand, neosalvarsan is readily soluble, only a small amount of sterile (distilled) water being used. We have tried using 150 c. c. of distilled water with each 0.9 gram of neosalvarsan, and gradually reducing the amount of water to between 40 and 50 c. c. to obtain greater concentration of the arsenic.

At present we have all patients needing antiluetic treatment come to the hospital on Wednesday afternoon. They are given calomel and salts. The next morning they are given intravenously 0.9 gram neosalvarsan in 40 c. c. distilled water. They are kept in bed the rest of the day and night, being given milk at night if they ask for it, and are not nauseated. With this procedure no case has ever had to return for treatment after receiving four injections and mixed treatment in the interim. The injections, as above stated, are given once a week. The patients leave the hospital Friday morning, and return the following Wednesday afternoon. We have never had any untoward symptoms, and this is largely attributed to a thorough evacuation of the bowels prior to the administration of the neosalvarsan. In several cases the blood has been reported negative for the Wassermann reaction, and yet the spinal fluid will give a positive result to the globulin content, to the leucocyte cell count, and to the Wassermann test.

Some of our cases have manifested symptoms of cerebrospinal infection, and in these an intravenous injection of neosalvarsan does not bring about the desired result. In these we resort to the use of salvarsanized serum, which is introduced through the spinal canal after performing a lumbar puncture and withdrawing a small amount of spinal fluid.

Briefly the method is: (1) Inject intravenously 0.9 gram neosalvarsan; (2) withdraw 50 c. c. blood one hour later; (3) centrifuge, remove about 12 c. c. serum; (4) add 18 c. c. of normal saline solution (or in proportion of 60 per cent saline, 40 per cent serum); (5) heat to 56° C. for one-half hour; (6) place on ice; (7) warm before using, withdraw 12 to 15 c. c. spinal fluid. Reinject the 30 c. c. of mixture slowly.

The neosalvarsan injected intravenously does not reach the subarachnoid space, and consequently the concomitant destruction of brain and cord by the spirochetæ and toxines is not prevented.

One case, A. F., suffering from an inability to control his bladder and rectum, and being bedridden, as well as mentally confused, was admitted December 1, 1913. His blood was taken and sent to Washington (Hygienic Laboratory) and the report was returned negative for the Wassermann reaction. A lumbar puncture was done, and the spinal fluid tested at the Harvard Medical School with a positive Wassermann finding, as well as a large globulin content and very many leucocytes. The patient was given the usual 0.6 gram neosalvarsan intravenously, and he showed signs of improvement in a few days. Was given mercurial inunctions and potassium iodide by mouth. One week later he was given a second intravenous injection of neosalvarsan, 0.9 gram, a lumbar puncture was performed, and the salvarsanized serum injected according to technique above given. A few days later patient was able to control both his bladder and bowels; appetite much improved; mental confusion disappeared so that patient could carry on a rational conversation. Prior to this time he was unable to say where he was or for how long he had been here. A third injection and introduction of the serum into the subarachniod space brought about even better results—patient out of bed walking on crutches and mind much clearer He is now able to walk unaided by crutches, and will receive another injection this week.

F. D., admitted August 1, 1913. Did not know where he was, could not tell his name (disoriented as to time, place, and person). Would fight anyone that offered to help him. Would do filthy things (evacuate his bowels in bed, or on the floor, and smear the feces over his clothes). His blood was reported negative for the Wassermann by the Hygienic Laboratory at Washington. Examination of the spinal fluid in Boston was positive for syphilis (Wassermann * * *, globulin increased, many leucocytes counted). Neosalvarsan 0.9 gram given intravenously, and the next day potassium iodide, saturated solution, gtts x, increasing gtts v daily, until gtts c T. I. D. Mercury salicylate gr. $\frac{1}{6}$, given intramuscularly, and increased to gr. ii three times a week. One week later he was given neosalvarsan 0.9 gram, and the serum injected into spinal canal. He

improved under this treatment, both mentally and physically; his static and motor ataxia less marked; could give his name and address correctly. Before the third injection he became delirious, and resorted to his former filthy habits, so he was moved into another room with a patient as attendant day and night. He threatened violence to the patient, and restraints were used to keep him in bed. A third injection and use of salvarsanized serum caused further improvement. Became more rational and offered to do some work in the ward. He continued to improve, and after the fourth treatment was entirely rational. He had a very large, indirect, inguinal (complete) hernia. Was fed well so as to strengthen him, and the hernia was operated upon. After recovery from the operation, employment on a boat going to Baltimore was obtained for him. Patients admitted since his discharge (October 27, 1913) have seen him and state that he is well.

E. P., admitted July 21, 1913, with a diagnosis of phlyctenular keratitis; Wassermann positive; was given an intravenous injection of neosalvarsan 0.9 gram, and within four days most of the conjunctivitis had disappeared. After the second injection, the corneal ulceration showed improvement and there was no hyperemia of the conjunctiva at all. He received four injections in all, and within one month after his admission he was discharged with an apparently normal eye, out of which he could see as well as out of the other organ.

J. B., readmitted September 27, 1913, with a diagnosis of phagedenic ulcer of penis, Wassermann positive. He was given two injections of neosalvarsan in the spring of the same year, but left to go to work before the ulcer healed. He has been given five more injections within the last six months, but no complete recovery is yet in sight. He is now receiving large doses of potassium iodide and mercury; the ulcer is almost healed, but has been as nearly well before, only to break down again.

It is difficult to estimate the time in days' hospital treatment saved by giving neosalvarsan in preference to mixed treatment. Some of the latter patients would remain for several months and receive mixed treatment, whereas others on same treatment would need to stay longer, but would leave the hospital against advice of attending physician at irregular times.

Detroit, Mich.—In a few of the cases in which salvarsan was given mercurial rubs were afterwards prescribed. Many of the cases of syphilis treated with neosalvarsan were kept in the hospital but one day, just sufficient time to note the reaction, if any. In fact, some of the cases were given the treatment and allowed to leave the hospital in an hour or two. After the first injection had been given and if no bad symptoms followed it, the second was frequently given and the patient allowed to leave the hospital in an hour or two.

There are cases that can be treated with neosalvarsan as out-patients, making a large saving in hospital treatment by the use of these remedies. Considering all forms of syphilis that are likely to apply for treatment at the hospital, I would estimate that the number of days' hospital treatment in such cases might be reduced by the use of neosalvarsan about one-half. I believe that mercury in some form is essential to success in the treatment of certain cases of syphilis and should be used after the injection of neosalvarsan in many, if not all cases of syphilis, and that the combined treatment, arsenic and mercury, is more effectual in syphilis than the single treatment with either.

Louisville Ky.—From the records of the station dating from July, 1909, there appears to have been a total of 90 cases of syphilis treated in this hospital. These cases remained under treatment for a total of 2,166 days. It is interesting to note that many of these cases returned to the hospital, some of them several times, for further treatment for syphilis; that others remained under continuous treatment for long periods—in one case for 214 days—and others for such periods as 35, 40, 45, 46, 62, 65, 66, 74, 77, 98, 110, and 154 days.

An examination of the histories of many of the cases shows that no decided benefit was derived from treatment by mercury and the iodides, inasmuch as the patients often returned after the lapse of several months or even weeks for further treatment. The first patient to receive salvarsan at this station was T. F., permit 95, admitted to hospital December 14, 1910; given one dose of salvarsan January 24, 1911, and a second dose February 2, 1911. This man was discharged February 14, 1911; improved, possible recovery. He had previously been under treatment in this hospital for syphilis a total period of 291 days.

Mobile, Ala.—It has been estimated for the purposes of this determination that under the old methods of treatment 60 days would represent a fair average, although it must be remembered that in dealing with the class of patients to whom relief is afforded by the Public Health Service there are very few who are willing to remain in the hospital long enough to take intelligent treatment of a protracted nature. Consequently it would appear that a large number of such have been leaving the hospital upon temporary cessation of symptoms, considering themselves as well. Treatment by salvarsan and neosalvarsan appears to represent the highest refinement in treatment of this condition, in view of the fact that frequently a single injection will accomplish the same results as many months of mercurial medication, and two or three injections at short intervals later will be a cure, so that, even though the same time be spent in the hospital, it is considered that the infectiousness of the individual

is greatly lessened, and the possibilities of further transmission of the infection are lessened.

During the past few months it has been the routine to administer at least one dose in all cases with a positive history in the presence of clinical symptoms, and where feasible two doses have been administered.

Providence, R. I.—Permit No. 145, M. S., 37, Portugese, admitted March 29 and discharged April 2, 1913. Brought in ambulance apparently suffering from acute mania of few hours' duration, was very violent and noisy, had to be tied and given opiates. Physical examination showed stigmata of syphilis and believing this the possible cause of symptoms and that in any case, salvarsan was indicated, this was given. Result, rapid improvement, patient was rational in 24 hours and left hospital apparently a well man on fifth day. This I consider a very remarkable case, and while it can not be affirmed that the rapid subsidence of symptoms was due to the treatment, it was apparently so.

Permit No. 147, H. F., 34, nativity Cape Verde Islands. In hospital recovering from pneumonia; readmitted April 4, diagnosis syphilis, tertiary; discharged April 4, 1913. Following his pneumonia patient had ulceration of throat and nose, thought at first to be tubercular. Progress rapid and alarming, in 10 days nose occluded, face badly swollen, throat inflamed, dyspnea increasing. Tuberculosis being excluded a diagnosis of tertiary syphilis was made. On account of patient's condition, the older remedies were tried for two days without result. Believing the patient would die unless the disease was checked, a full dose of salvarsan was given on April 4. The result might well be called magical. In 24 hours instead of being propped up in bed, struggling for air, weak and frightened, he was smiling and demanding something to eat. The following day, in spite of my protests, he left the hospital, saying he was well. In 48 hours his nasal breathing had been restored and the swelling in throat and of face much reduced.

Permit No. 157, A. N., 51, Norway, admitted May 12, discharged June 2, 1913. Chronic enlarged and painful glands of left groin. Wassermann positive. Two injections neosalvarsan at 10 days' interval. Result, pain entirely relieved, swelling reduced.

Permit No. 45, C. R., 47, Cape Verde Islands. Applied for salvarsan. History, syphilis 10 years, lately pains in head, neurasthenic, Wassermann positive. Given neosalvarsan. Mental state improved, claimed pain less, returned to work satisfied. This man was getting the hospital habit, so probably salvarsan has saved many hospital days for him.

Seattle, Wash.—The Public Health Service having only a contract station at Seattle, Wash., syphilitic patients needing hospital treatment were formerly sent to Port Townsend, as a rule, on account of

the length of time such cases usually required to remain in the hospital. Since the introduction of salvarsan and neosalvarsan, relief from symptoms which send these patients to the hospital is so prompt that very little hospital treatment is required other than that necessary for the administration of these drugs, unless we are dealing with old standing cases where there is already considerable destruction of tissue, and even here the time in the hospital, in my experience, is greatly reduced.

The records of our hospital patients show that from July 1, 1908, to January 1, 1911, 15 patients were admitted for syphilis and a total of 225 days' treatment was furnished them, or an average of 17 days for each patient. From January 1, 1911, to July 1, 1913, 94 patients were admitted and treated with salvarsan or neosalvarsan, remaining in the hospital a total of 236 days, or an average of 2½ days each, as compared with 17 days each under the old system of treatment. The majority of these latter cases were in the secondary stage of the disease, the time when hospital treatment is usually most apt to be necessary.

Under the old methods of treatment the average sailor is what may be known as a periodical patient. He comes back and each time he usually stays a little longer, until he ends up in many cases with an old leg ulcer, locomotor ataxia, cirrhosis of the liver, gumma, or some other condition which renders him if not a continuous at least a recurrent public charge. The best observers to-day believe and teach that if syphilis is efficiently and persistently treated in the earlier stages 95 per cent or more of such distressing end results as are mentioned above may be prevented absolutely. Furthermore, one of the greatest obstacles formerly encountered in the treatment of this disease, namely, the two or three years' daily continuous treatment, is removed. Nothing so appeals to the patient, especially the seafaring man, as the fact that he can take the major portion of his medicine in from four to six treatments of a few minutes' duration.

A comparison of the course of this disease under the old and the new treatment may be illustrated by the following brief notes of a series of cases.

O. N., Swede, aged 49 years, suffering from locomotor ataxia, one of the terminal stages of syphilis; was treated 15 years previously for syphilis, but did not continue treatment as long as advised; suffers a great deal, and can not work steadily; from July 12, 1909, to July 5, 1913, was in the hospital in Seattle at different times a total of 46 days, and each time he was transferred to the hospital at Port Townsend as soon as he was able to travel. The Townsend records are not available for this report, but it is known that he spent months in the hospital there. The only other case of locomotor ataxia admitted here during the last five years was P. K. He was first admitted February 21, 1912, and was found to be in the early stages of this terminal condition of syphilis. On his first admission it was believed that

neosalvarsan could be safely administered, and after the dangers were explained to him, he was given graduated doses, remaining in the hospital from February 21 to March 28, or 35 days; he returned for subsequent treatment on April 7, 1912, and June 24, 1912, remaining in the hospital only one day each time, or just long enough to recover from the immediate effects of full doses of neosalvarsan.

A. C. was admitted to the hospital December 2, 1910, for a syphilitic ulcer of the leg, which incapacitated him; he was discharged 21 days later and treatment continued at the outpatient office for about 10 weeks. Nearly one year later this patient returned in almost as bad condition as when first treated. He was sent to the hospital and given salvarsan, and after four days discharged and treated at the outpatient office, the ulcer healing in about 4 weeks.

Of the 94 patients admitted to the hospital and treated with salvarsan and neosalvarsan, 61 were admitted for secondary lesions. If we compare the time in hospital of these patients with that of the same class of patients treated previous to the advent of salvarsan, we find that the time is reduced at least 14 days each for this period of observation, or about 82 per cent.

Savannah, Ga.—Of especial interest in this connection is the history of C. J., permit No. 121, admitted November 26, 1908, with a diagnosis of syphilis, secondary, the disease having been contracted in 1903. This was a most severe and obstinate case, totally incapacitating the patient for work, not yielding to any of the methods of treatment applied. After having received hospital relief at this station since November 26, 1908, he was given an injection of salvarsan on June 17, 1911. This was the first injection of salvarsan given at this station. This injection was followed by great improvement in the patient's condition, and he was subsequently given two more injections July 25, 1911, and August 25, 1911. Considerable improvement followed and he was discharged on September 20, 1911, markedly improved and able to return to work. It is believed that without treatment with salvarsan, this patient would have been in constant need of hospital treatment as long as he would have lived.

Lieut. Col. Gibbard and Maj. Harrison, of the British Army, have compiled the following table from the records of the War Office:

Treatment.	Total cases.	Average number of days in hospital on first admission.	Clinical relapses.				Percentage of clinical relapses.	Average time lost by each man in days.		
			Once only.	Twice only.	Three or more times.	Total number which relapsed.		In hospital.	Attending as an outpatient.	Total.
Mercury alone	371	42.0	151	115	49	315	83.0	66.2	17.6	83.8
Mercury and salvarsan	152	23.2	6	0	0	6	3.9	25.2	15.8	41.0

The special points to which they draw attention in this table are:

(1) The very marked reduction in the number of clinical relapses shown by the salvarsan as compared with the exclusively mercurial cases; and (2) the great reduction in the average number of days lost by each soldier, especially in hospital. It will be seen that the salvarsan cases spent an average of 41 days less in hospital during the first year than the exclusively mercurial. Considering that about 2,000 fresh cases of syphilis are admitted every year to Army hospitals, we may reasonably expect that without any improvement on present methods the routine use of salvarsan will effect a total annual saving of between 70,000 and 80,000 hospital days. At present the total number of admissions for syphilis to British Army hospitals yearly is about 4,000, but only half of these are fresh cases. On the basis of this table the routine treatment of syphilis with salvarsan and mercury will reduce the number of relapses so much that the total admissions to hospitals for syphilis should be reduced from over 4,000 to about 2,300.

Browning, in speaking of the treatment of syphilis, says:

Whereas the function of hospitals should be not merely to house cases of sickness, but also to treat them, there is nowadays the tendency for such institutions to do neither the one nor the other with syphilitic patients. Cases of acquired syphilis are, at most, treated in the outdoor department with pills, powders, or mercurial solutions—a form of therapy which only very slowly extinguishes infectivity, and, as usually carried out, probably fails to effect cure in more than a small proportion of cases. Now, there can be no doubt that for the safety of the general community the infectivity of cases of recently acquired syphilis should be abolished as rapidly as possible. This can be effected with great certainty and rapidity by admitting the patient into hospital for periods of two days on five or six occasions, and giving him intravenous injections of salvarsan; in addition, he should receive systematic courses of mercurial injections or inunctions at the out-patient department. Precisely how long a time will be necessary to abolish infectivity by such treatment has not been definitely ascertained. It is well known that the syphilitic patient with tertiary lesions is usually noninfective and this is probably due in great part to the small number of spirochætes which he harbors. Applying the same point of view to cases treated energetically with salvarsan, it is most likely that they are also noninfective within a few weeks afterwards; but if complete sterilization has not been effective a recrudescence may occur with no doubt renewed infectivity. The prolonged subsequent treatment by mercurial injections or inunctions aims at preventing this latter possibility.

Emory makes the following statement regarding the prospect of cure of syphilis:

At the very outset of the disease, before the spirochætes have generalized, it can be cut short once and for all by the excision of the chancre; the exact length of time after infection during which this is possible can not be stated with accuracy, but it is quite short, and has terminated long before the Wassermann reaction. And after generalization has occurred there is no object whatever in performing excision; the idea that the patient will derive benefit from a cutting off of a further supply of spirochætes from the primary lesion is quite mistaken.

During the late primary and early secondary stages the disease is readily curable, and many patients who have received energetic treatment after the development of undoubted secondary symptoms, remain for many years free from all reminders of the disease, and their blood and cerebrospinal fluid show no Wassermann reaction.

In the later stages, after the late secondary symptoms, and even more after the development of tertiary symptoms, the disease enters into a stage in which the prospect of cure in the modern sense—that is, the complete destruction of every spirochæte in the body—becomes gradually more and more difficult. Some, in fact, go further than this, and say that if a patient has once developed secondary symptoms, cure is

impossible. I think this is an entirely mistaken and unnecessarily pessimistic view, and one that is to be regarded merely as a reaction from the too optimistic views which were once held when salvarsan was first introduced, and we hoped for a *therapia magna sterilisans* after a single dose of the drug.

* * * * * * *

The one and only certain proof of * * * [cure] is the possibility of reinfecting the patient; this shows that his tissues have returned to their normal degree of sensitiveness, which can not happen if there are spirochætes still in the body. This test is, of course, impracticable, and we must look about for something else. Whether the luetin reaction will help us in the future is as yet unknown, and at the present time we have to fall back on the Wassermann reaction. Under what circumstances does a negative reaction indicate cure?

To begin with, it is quite useless to draw any inference from its absence unless we know that it has been present comparatively recently. If we do not remember this, we may find that we are dealing with one of the cases in which it has spontaneously disappeared in the tertiary stages, as I have already described, whilst the disease is still active. Then we must remember the effect of treatment; mercury and salvarsan will remove the reaction without necessarily curing the disease, the negative phase (if I may use the expression) lasting for so long a time as a year. Taking these facts into consideration, I think we may deduce this as a working rule: If, in a patient whom we know to have had a Wassermann reaction, we find it remains absent for a year after the cessation of treatment, we may assume with a high degree of probability that he is completely and radically cured, and I think we shall very seldom be mistaken. If we want a higher degree of certainty still, we may give an injection of salvarsan, and see if the reaction reappears, and if it does not do so, I believe the chain of evidence is complete.

Safety of Salvarsan.

Prof. Ehrlich, in discussing the mortality after the use of salvarsan before the International Medical Congress, August 11, 1913, observed that chloroform was annually responsible for a much higher percentage of deaths than salvarsan, and he was—

convinced that the small number might be even further reduced by instituting a careful search in all cases about to be injected for the contraindications—for example, renal inefficiency, Addison's disease, status lymphaticus, and advanced cancer.

The very occasional occurrence of deafness four to five hours after an injection was due to swelling and compression of the auditory nerve in its bony canal, whilst late deafness with commencing cerebral symptoms probably indicated the advance of a basal meningitis, and were manifestations of a true Yarisch-Herxheimer phenomenon. Further injections in such delayed cases (two to five days) would be to pour oil on the fire, accelerate the advance of the meningitis, and kill the patient.

Caesar states that he believes salvarsan has a toxic action on the cerebral capillaries, tending to paralyze their constrictile elements. For this reason he thinks it should be not used where there is arteriosclerosis, or capillary degeneration due to chronic intoxications, particularly alcohol and existing disease of the central nervous system.

Ebright gives the contraindications to the use of salvarsan in a paper read before the California Academy of Medicine. He says:

Certain organic diseases are an absolute contraindication to the use of salvarsan, while the presence of others requires its use with caution. According to Ehrlich, the triad, aortitis, coronary sclerosis, and myocarditis should absolutely contraindicate

the use of the drug. The elaboration of that rule demands the exercise of caution where there is disease of the blood vessels, all myocardial diseases of the heart, or nephritis, either acute or chronic. Advanced diseases of the cerebrospinal system, as tabes dorsalis, where considerable damage has already been accomplished, are contraindications, and also in those conditions where syphilitic meningitis comes into question it should be used with great care. Death has followed its use repeatedly in cerebrospinal lesions, at which the autopsy showed leptomeningitis, generalized congestion of the brain, or a reaction of the syphilitic focus involving a vital center. General paresis is a general contraindication to the use of salvarsan for similar reasons. Disease of the optic or auditory nerve of central origin probably should be considered a contraindication. J. F. Schamberg collected 15 cases of optic neuritis following salvarsan and 19 cases of auditory nerve disturbance in something like 50,000 cases. It may be that this collection was incomplete. In addition, accidents may happen from salvarsan without appreciable cause. Mann reports a death from salvarsan in a strong patient who had always been well. Three days after intravenous injection the patient became unconscious, with complete loss of all recollection and sensibilities. This lasted three days and gradually subsided. Kannengiesser observed in a robust butcher of 29 epileptiform convulsions three hours after injection, followed by death. Autopsy failed to show satisfactory explanation. Gaucher reports a corpulent man who upon examination showed no cardiac, renal, or cerebral trouble, and four days after 0.6 gram of salvarsan the patient was found lying in his room completely unconscious and moving convulsively. The following day he was in the same stupor, convulsive crises recurred, cyanosis, perspiration, rapid pulse, a rise of temperature to 105° F.; at autopsy a leptomeningitis. Another case was of a man of 21 who at autopsy showed generalized congestion of the brain and lungs.

Schmitt stated at the same meeting:

The reactions of patients to salvarsan should be divided into two classes: One, the very definite arsenical poisoning, and the other, the so-called Herxheimer reactions, whether on the skin or in the internal organs. It seems that patients with liver and central nerve involvement undoubtedly react stronger to salvarsan than other classes of luetics. This is manifested mainly by a flare-up of the lesions. The hepatitis we have in lues is accompanied by a marked increase of interstitial tissue. There is a sudden breaking down of this interstitial tissue, and the bringing of salvarsan into close contact with the foci of spirochætes would undoubtedly cause some of the reaction in this particular instance.

As to the unconsciousness, we know definitely that leptomeningitis is common, and when mercury has been given with salvarsan and immediately following it, the percentage of cases of unconsciousness, severe headaches, and other conditions referable to the central nervous system are markedly less. I recall an instance of a man who had an infection 41 years prior to the appearance of the hepatitis. The first dose of salvarsan brought on a rather severe reaction, so much so that we were afraid of the outcome. We used salvarsan a second time, following it with mercury intravenously, without any reaction. We can infer from this and other evidence that we have a definite reaction from the luetic source as well as from the arsenical condition.

Lieut. Col. Gibbard and Maj. Harrison, quoted above, remark that—

The question of death immediately following an injection of salvarsan is one which is naturally of considerable interest to all of us. Our own experience in this respect has been very fortunate, since in over 2,500 intravenous injections we have not experienced any fatality. From a consideration of the literature on this subject it seems to us that fatalities may be divided into three classes: (a) Those which could have been avoided by attention to well-known contraindications and by careful

technique and after treatment; (b) deaths due to pulmonary embolism; and (c) those in which a series of epileptiform convulsions followed by death has occurred on the third to the fifth day after the injection; the explanation of the last named is still in dispute. We can serve no useful object by discussing the first two of these, but we would like to offer our views on the third class, in the hope that we may assist in arriving at a correct explanation of the cause of death in these cases, and possibly at some agreement as to the best means of preventing it. There are two explanations of these fatalities. One is that they are due to an exacerbation of cerebral syphilis, a Yarisch-Herxheimer reaction in the central nervous system; and the other, that they are due to salvarsan poisoning. It is urged in favor of the first of these explanations that the patients are almost always in the late primary or early secondary stage, when it is so common for the meninges to be affected, and that the cerebral changes found post mortem are consistent with the view that death is due to poisoning with endotoxins of *Spirochæta pallida*. It must be admitted, however, that if death is due to the release of a large amount of spirochæte endotoxins, it is extraordinary that this should occur so extremely rarely after the first injection, and that it should have such a long incubation period as two or even five days. Our experience of the Yarisch-Herxheimer reaction as it is exhibited in other parts of the body shows that it occurs within a few hours of the first injection.

Further, we would expect that an exacerbation of cerebral syphilis so severe as to cause death would surely be accompanied by profound pathological changes in the cerebrospinal fluid. By the kindness of Capt. A. T. Frost, R. A. M. C., we have had an opportunity of examining the cerebrospinal fluid and organs of a patient who died in epileptiform convulsions on the fourth day after an injection of salvarsan. The particulars of the case are as follows: The patient, a soldier, aged 20, suffering from early secondary syphilis, but without any headache, was treated with two injections of 0.6 grm. salvarsan, with an interval of two weeks between the two injections. The urine was tested before each injection and found to be normal. No reaction followed either injection beyond a slight and transient headache after the second. The correctness of the technique of the second injection is vouched for by the fact that Capt. Frost administered it himself, and seven other patients injected on the same day suffered no reaction whatever. The symptoms commenced on the morning of the fourth day with severe vomiting, which was followed by a series of epileptiform convulsions, and the patient died in coma 12 hours later. Capt. Frost removed 18 c. c. of cerebrospinal fluid some hours before death, and it is possible that it may have been slightly contaminated with blood. He found in it 20 cells per cubic centimeter, but a differential count was not made. The further tests were carried out by one of us, and the reaction of the fluid to the Wassermann, Nonne, Lange, and Noguchi tests, was in each case negative. For the Wassermann test an amount of fluid corresponding to 10 times the quantity of blood serum which is usually taken, was used. Beyond the slight increase in cells, therefore, there was no evidence of syphilitic change in the cerebrospinal fluid of this case. The portions of brain sent to us were taken from a temporosphenoidal lobe and internal capsule, but in neither of these were we able to find microscopically any evidence of syphilis, nor were there any capillary hemorrhages such as have been reported by other workers. On the other hand, the renal tubules were filled with blood cells. It seems to us that we must recognize the possibility of an idiosyncrasy to salvarsan in a very small minority of patients. Fortunately, this idiosyncrasy does not become dangerous unless the salvarsan is repeated in full doses at intervals which are too frequent, and for this reason we are now averse to repeating full doses of salvarsan after intervals which are shorter than one month. We admit that the risk of death after more frequent repetition is very slight, but if the same object is served by spacing the injections well out and filling the intervals with mercurial injections, there is no point in running any risk.

In speaking of the occurrence of cranial nerve disturbances after salvarsan injection, they say:

> The lesson that we learn from these affections is that the initial course of salvarsan must be prolonged and thorough; that careful subsequent observation must on no account be neglected; and if unfortunately the patient subsequently shows signs of cranial nerve trouble no time must be lost before commencing salvarsan treatment, since delay involves a risk of irreparable damage to the affected nerve.

Conclusions.

There is no question that salvarsan has been of great benefit to mankind and that much suffering has been relieved by its use and the number of hospital days required in the treatment of syphilis greatly reduced. Many persons who were partially or totally disabled have regained their health after its administration, and have returned to work. The deaths after salvarsan, considering the care with which the substance has to be given and its high content of arsenic, are exceedingly few; but caution should be employed in using it in tertiary forms of the disease. As an idiosyncrasy to salvarsan is present in a small minority of patients, it is advisable, where repeated injections are employed, to test the urine to decide the duration of the arsenic elimination after each dose. Fewer bad effects have been observed where mercury in some form is used between the salvarsan injection.

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